UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,760	10/03/2003	Alan J. Heeger	327823-1050	7598

38706 7590 08/07/2006

FOLEY & LARDNER LLP
1530 PAGE MILL ROAD
PALO ALTO, CA 94304

EXAMINER	
CROW, ROBERT THOMAS	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.** 10/678,760	**Applicant(s)** HEEGER ET AL.	
	Examiner Robert T. Crow	**Art Unit** 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2006*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *53-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☒ Other: *Notice to Comply*.

SUPPLEMENTAL OFFICE ACTION

1. The previous Office Action, filed 23 May 2006, is withdrawn.

2. This Supplemental Office Action is being provided to correct the numbering of the claims rejected under 35 USC 103(a). Page 19 of the previous Office Action, filed 23 May 2006, listed claims 37-42, 44, and 45-50 as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Sorge et al (U.S. Patent No. 6,350,580, issued 26 February 2002), and also listed claim 37 as the first claim rejected. Claims 36-42, 44, and 45-50 are unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Sorge et al (U.S. Patent No. 6,350,580, issued 26 February 2002), and the first rejected claim is 36, not 37.

3. The remaining text of the Office Action is unchanged.

Election/Restrictions

Applicant's election of Group I in the reply filed on 5 April 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 53-56 are withdrawn. Claims 1-52 are currently under prosecution.

Information Disclosure Statement

The Information Disclosure Statement filed 5 April 2006 is acknowledged. However, only the Abstracts of documents CN 1422960 and CN 1422961 are being considered because English translations of the remainder of the documents have not been provided.

Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosure.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically, the Specification discloses nucleotide sequences in paragraphs 0073 and 0085. However, the sequences do not have SEQ ID NOS. In addition, a paper of compact disc copy of a "Sequence Listing" has not been provided, nor has a computer readable form (CRF) containing the "Sequence Listing" has been provided. Finally, a statement that the "Sequence Listing" content of the paper or compact disc "Sequence Listing" is the same as the content of the computer readable copy.

For compliance with sequence rules, it is necessary to include all sequences in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a string of particular bases or amino acids, and that otherwise meets the criteria of CFR 1.821(a), must be set forth in the "Sequence Listing." See MPEP 2422.03.

While the Examiner has made every attempt to check the Specification for sequence compliance, Applicant is **required** to carefully check the entire Specification for any and all issues regarding sequence compliance.

For the response to this Office Action to be complete, Applicant is **REQUIRED** to comply with the Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Failure to comply with the Requirements will be considered **nonresponsive**.

Specification

The disclosure is objected to because of the following informalities: the nucleotide sequences in paragraphs 0073 and 0085 do not have SEQ ID NOS. .

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 10-15, 17, 19, 21, 24, 25, 28, and 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 5, 10, 15, 24, and 25 are indefinite in claim 5, which recited the limitation "claims 1-4" in line 1 of claim 5. The dependency of the claim is unclear.

2. Claims 11-15, 17, 19, 21, 25, 28, and 30 are indefinite in claims 11-15, which recite the limitation "the result" in line 2 of each of claims 11-15. There is insufficient antecedent basis for this limitation in each of the claims. It is suggested that the word "the" be changed to "a" in each of the claims. Claims 11-15, 17, 19, 21, 14, 25, 28, and 30 are also indefinite in claims 11-15, which recite the limitation "the polynucleotide" at the end of each of claims 11-15. It is unclear if "the polynucleotide" refers to the immobilized polynucleotide probe or if "the polynucleotide" refers to the polynucleotide target.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-7, 9-12, 14-19, 22-25, 33, and 35 rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001).

Regarding claim 1, Lee et al teach a detector for determining the presence of a target polynucleotide having a target nucleotide sequence (Abstract) comprising an electrode capable of sensing redox events in a redox moiety (e.g., electrodes in a microreaction vessel; page 19, line 36-page 20, line 8), and an immobilized probe (e.g., a probe immobilized on an electrode; page 4, line 35-page 14, line 2), the probe carrying a redox moiety (page 12, lines 5-9) and having a probe nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9) and having a first configuration in the absence of hybridization with the target polynucleotide, which located the redox moiety in a first position relative to the electrode and having a second configuration, in the presence of hybridization with the target polynucleotide, which locates the redox moiety in a second position relative to the electrode (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31), said first and second positions giving rise to distinguishable redox events detectable by the electrodes (e.g., hybridization results in a change in the redox properties of a pair of labels that are recorded electrochemically; page 12, lines 5-9).

Regarding claim 2, Lee et al teach the detector of claim 1 wherein the first position is closer to the electrode is that the second position (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization to a target, a pair of labels are separated [page 3, lines 24-31], wherein the redox moiety of claim 1 is the label within the pair of labels that is further away from the electrode after hybridization).

Regarding claim 4, Lee et al teach the detector of claim 1 wherein the probe is immobilized on the on the electrode at a position distant from the redox moiety (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 5, Lee et al teach the detector of claim 1 wherein the electrode is capable of inducing redox events in the redox moiety (e.g., application of an electrochemical potential is applied to induce hybridization [page 17, lines 19-32], wherein the hybridization results in a change in the redox properties of a pair of labels that are recorded electrochemically; page 12, lines 5-9).

Regarding claim 6, Lee et al teach the detector of claim 1 wherein the first configuration comprises internal hybridization between two regions in the polynucleotide probe (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence; page 3, lines 24-31).

Regarding claim 7, Lee et al teach the detector of claim 2 wherein the first configuration comprises internal hybridization between two regions in the polynucleotide probe (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence; page 3, lines 24-31).

Regarding claim 9, Lee et al teach the detector of claim 4 wherein the first configuration comprises internal hybridization between two regions in the polynucleotide probe (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence; page 3, lines 24-31).

Regarding claim 10, Lee et al teach the detector of claim 5 wherein the first configuration comprises internal hybridization between two regions in the polynucleotide probe (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence; page 3, lines 24-31).

Regarding claim 11, Lee et al teach the detector of claim 6 wherein the second configuration comprises a disrupted internal hybridization as the result of hybridization between a region in the polynucleotide probe and a complementary region in the polynucleotide (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31).

Regarding claim 12, Lee et al teach the detector of claim 7 wherein the second configuration comprises a disrupted internal hybridization as the result of hybridization between a region in the polynucleotide probe and a complementary region in the polynucleotide (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31).

Regarding claim 14, Lee et al teach the detector of claim 9 wherein the second configuration comprises a disrupted internal hybridization as the result of hybridization between a region in the polynucleotide probe and a complementary region in the polynucleotide (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31).

Regarding claim 15, Lee et al teach the detector of claim 10 wherein the second configuration comprises a disrupted internal hybridization as the result of hybridization between a region in the polynucleotide probe and a complementary region in the polynucleotide (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31).

Regarding claim 16, Lee et al teach the detector of claim 6, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 17, Lee et al teach the detector of claim 11, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 18, Lee et al teach the detector of claim 7, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 19, Lee et al teach the detector of claim 2, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 22, Lee et al teach the detector of claim 9, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 23, Lee et al teach the detector of claim 14, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 24, Lee et al teach the detector of claim 10, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 25, Lee et al teach the detector of claim 15, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 33, Lee et al teach the detector of claim 1 wherein the electrode comprises a metal (page 8, lines 15-21).

Regarding claim 35, Lee et al teach the detector of claim 1 wherein the redox moiety is ethidium bromide (page 15, lines 5-15).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1, 3, 8, 13, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Fan et al (U.S. Patent Application Publication No. US 2002/0006617 A1, published 17 January 2002).

Regarding claim 3, Lee et al teach a detector for determining the presence of a target polynucleotide of claim 1 having a target nucleotide sequence (Abstract) comprising an electrode capable of sensing redox events in a redox moiety (e.g., electrodes in a microreaction vessel; page 19, line 36-page 20, line 8), and an immobilized probe (e.g., a probe immobilized on an electrode; page 4, line 35-page 14, line 2), the probe carrying a redox moiety (page 12, lines 5-9) and having a probe nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9) and having a first configuration in the absence of hybridization with the target polynucleotide, which located the redox moiety in a first position relative to the electrode and having a second configuration, in the presence of hybridization with the target polynucleotide, which locates the redox moiety in a second position relative to the electrode (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31), said first and second positions giving rise to distinguishable redox events detectable by the electrodes (e.g., hybridization results in a change in the redox properties of a pair of labels that are recorded electrochemically; page 12, lines 5-9). Lee et al are silent with respect to the second position having the second position closer to the electrode.

However, Fan et al teach immobilized target nucleic acids (paragraph 0078) and rolling circle probes that bind the target nucleic acid (paragraph 0094, wherein the hybridization immobilizes the probe) wherein the probe has a label sequence (number 150 of Figure 10 and paragraph 0014), wherein upon hybridization the label moves closer to the surface (i.e., the rolling circle probe hybridizes one end first, thereby becoming immobilized, followed by hybridization of the second end, which brings the label sequence closer to the surface by locking it in open circle form) with the added advantage that rolling circle probes allow polymerase to extend the probe repeatedly (paragraph 0091).

It would therefore have been obvious to a person or ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al with the probes as taught by Fan et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in repeated extension of the probe as explicitly taught by Fan et al (paragraph 0091).

Regarding claim 8, the detector of claim 3 is discussed above. Lee et al teach also the detector wherein the first configuration comprises internal hybridization between two regions in the polynucleotide probe (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence; page 3, lines 24-31).

Regarding claim 13, the detector of claim 8 is discussed above. Lee et al teach the detector wherein the second configuration comprises a disrupted internal hybridization as the result of hybridization between a region in the polynucleotide probe and a complementary region in the polynucleotide (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31).

Regarding claim 20, the detector of claim 8 is discussed above. Lee et al also teach the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 21, the detector of claim 13 is discussed above. Lee et al also teach the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

3. Claims 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) as applied to claims 1, 6, and 11 above, and in view of Egholm et al (U.S. Patent No. 6,451,588 B1, issued 17 September 2002).

Regarding claims 26-27, the detectors of claims 1, 6, and 11 are discussed above. Lee et al are silent with respect to internal hybridization in the second conformation.

However, Egholm et al teach immobilized nucleic acid probes (column 15, lines 40-53) wherein upon hybridization to the target, the probe comprises internal hybridization (e.g., Figures 4C and 4D, where the probe is a pair of probes [Figure 4C] that, upon hybridization to target 20, has a hybridization region maintained between probes 44 and 46; column 12, lines 1-13) with the added advantage of allowing use of two low-complexity libraries having less that 0.005% of the probes required by a single high-complexity library (column 14, lines 24-47).

It would therefore have been obvious to a person or ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al with the probes as taught by Egholm et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing use of two low-complexity libraries having less that 0.005% of the probes required by a single high-complexity library as explicitly taught by Egholm et al (column 14, lines 24-47).

4. Claims 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) and Fan et al (U.S. Patent Application Publication No. US 2002/0006617 A1, published 17 January 2002) as applied to claims 1, 3, 8, and 13 above, and in view of Egholm et al (U.S. Patent No. 6,451,588 B1, issued 17 September 2002).

Regarding claims 29-30, the detectors of claims 1, 3, 8, and 13 are discussed above. Lee et al and Fan et al are silent with respect to internal hybridization in the second conformation.

However, Egholm et al teach immobilized nucleic acid probes (column 15, lines 40-53) wherein upon hybridization to the target, the probe comprises internal hybridization (e.g., Figures 4C and 4D, where the probe is a pair of probes [Figure 4C] that, upon hybridization to target 20, has a hybridization region maintained between probes 44 and 46; column 12, lines 1-13) with the added advantage of allowing use of two low-complexity libraries having less that 0.005% of the probes required by a single high-complexity library (column 14, lines 24-47).

It would therefore have been obvious to a person or ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al and Fan et al with the probes as taught by Egholm et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing use of two low-complexity libraries having less that 0.005% of the probes required by a single high-complexity library as explicitly taught by Egholm et al (column 14, lines 24-47).

5. Claims 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) and Fan et al (U.S. Patent Application Publication No. US 2002/0006617 A1, published 17 January 2002) as applied to claims 1 and 3 above, and further in view of Rothberg et al (U.S. Patent Application Publication No. US 2002/0012930 A1, published 31 January 2002).

Regarding claims 31 and 32, the detectors of claims 1 and 3 are discussed above. While Fan et al teach rolling circle probes (paragraph 0094), neither Lee et al nor Fan et al teach loops in the target in the second conformation.

However, Rothberg et al teach rolling circle probes having a loop in the target (e.g., Figure 1D, wherein the hybridized circular molecule leaves a loop [i.e., the gap I Figure 1D] in the immobilized target) with the added advantage that the rolling circle probes allow isothermal amplification of thousands of copies of the nucleic acid (paragraph 0087).

It would therefore have been obvious to a person or ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al and Fan et al with the probes as taught by Rothberg et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing isothermal amplification of thousands of copies of the nucleic acid as explicitly taught by Rothberg et al (paragraph 0087).

6. Claims 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) as applied to claim 1 above, and further in view of Hashimoto (U.S. Patent Application Publication No. US 2001/0024788 A1, issued 27 September 2001).

Regarding claim 34, the detector of claim 1 is discussed above. While Lee et al also teach the detector of claim 33 wherein the electrode comprises a metal (page 8, lines 15-21), Lee et al are silent with respect to gold.

However, Hashimoto teaches a nucleic acid carrier for electric detection of nucleic acids (Abstract) comprising gold electrodes and immobilized thiolated nucleic acids with the added advantage that gold is preferable for immobilizing sulfur-bearing nucleic acids because of the high affinity of gold for sulfur (paragraph 0032).

It would therefore have been obvious to a person or ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al with the gold electrodes as taught by Hashimoto with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in high affinity immobilization of nucleic acids to the electrodes as explicitly taught by Hashimoto (paragraph 0032).

7. Claims 36-42, 44, and 45-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Sorge et al (U.S. Patent No. 6,350,580, issued 26 February 2002).

Regarding claim 36, Lee et al teach a detector for determining the presence of a target polynucleotide having a target nucleotide sequence (Abstract), said detector comprising an electrode capable of sensing redox events in a redox moiety (e.g., electrodes in a microreaction vessel; page 19, line 36-page 20, line 8), and an immobilized probe (e.g., a probe immobilized on an electrode; page 4, line 35-page 14, line 2), the probe carrying a redox moiety (page 12, lines 5-9) and having a probe nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9). While Lee et al teach probes comprising hairpins (e.g., molecular beacons; page 3, lines 24-31), and hybridization to the target resulting in a change in the redox properties of a pair of labels that are recorded electrochemically (page 12, lines 5-9), Lee et al do not teach first through fifth regions forming hairpins between the second and fourth regions and the third and fifth regions (i.e., pseudo-knots).

However, Sorge et al teach immobilized molecular beacons (column 39, lines 1-2) wherein the probes are pseudoknots (column 4, lines 25-30 and lines 45-48 and Figure 3H) wherein upon target binding to the probe the secondary structure of the probe changes with the added advantage that to disruption of the pseudoknot allows detection (column 4, lines 10-19).

It would therefore have been obvious to a person or ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al with the pseudoknot probes as taught by Sorge et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing detection as explicitly taught by Sorge et al (column 4, lines 10-19).

Regarding claim 37, the detector of claim 36 is discussed above. Lee et al also teach means for detecting electron transduction between the electrode and the redox moiety when the hairpin (e.g., the hybridization results in a change in the redox properties of a pair of labels that are recorded electrochemically; page 12, lines 5-9).

Regarding claim 38, the detector of claim 37 is discussed above. Lee et al also teach means for inducing electron transduction between the electrode and the redox moiety when the hairpin is formed (e.g., application of an electrochemical potential is applied to induce hybridization; page 17, lines 19-32).

Regarding claim 39 the detector of claim 38 is discussed above. Lee et al also teach the first region is at one end of the probe (e.g., one end is immobilized to the electrode; page 4, line 35-page 14, line 2).

Regarding claims 40 and 41 the detector of claim 38 is discussed above. Sorge et al also teach the fifth region is at one end of the probe, wherein the end is the second end (Figure 3H).

Regarding claim 42, the detector of claim 36 is discussed above. Lee et al also teach the electrode comprises a metal (page 8, lines 15-21).

Regarding claim 44, the detector of claim 36 is discussed above. Lee et al also teach the redox moiety is ethidium bromide (page 15, lines 5-15).

Regarding claim 45, Lee et al teach a detector for determining the presence of a target polynucleotide having a target nucleotide sequence (Abstract), said detector comprising an electrode capable of sensing redox events in a redox moiety (e.g., electrodes in a microreaction vessel; page 19, line 36-page 20, line 8), and an immobilized probe (e.g., a probe immobilized on an electrode; page 4, line 35-page 14, line 2), the probe carrying a redox moiety (page 12, lines 5-9) and having a probe nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9). While Lee et al teach probes comprising hairpins (e.g., molecular beacons; page 3, lines 24-31), and hybridization to the target resulting in a change in the redox properties of a pair of labels that are recorded electrochemically (page 12, lines 5-9), Lee et al do not teach first through third regions forming loops (i.e. cloverleaf structures).

However, Sorge et al teach immobilized molecular beacons (column 39, lines 1-2) wherein the probes are cloverleaf structures (column 4, lines 25-30 and lines 45-48 and Figure 3G). Sorge et al also teaches in Figure 4 that upon hybridization, portions of the hairpin probe remain unhybridized; therefore, when a target hybridizes a cloverleaf structure, the unhybridized portion of the probe is disrupted and forms a new loop with the remaining nucleotides not already in a stem. Sorge et al also teach that target binding to the probe changes the secondary structure of the probe to advantageously allow detection (column 4, lines 10-19).

It would therefore have been obvious to a person or ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al with the cloverleaf probes as taught by Sorge et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing detection as explicitly taught by Sorge et al (column 4, lines 10-19).

Regarding claim 46, the detector of claim 45 is discussed above. Lee et al also teach means for detecting electron transduction between the electrode and the redox moiety when the hairpin (e.g., the hybridization results in a change in the redox properties of a pair of labels that are recorded electrochemically; page 12, lines 5-9).

Regarding claim 47, the detector of claim 46 is discussed above. Lee et al also teach means for inducing electron transduction between the electrode and the redox moiety when the hairpin is formed (e.g., application of an electrochemical potential is applied to induce hybridization; page 17, lines 19-32).

Regarding claim 48 the detector of claim 47 is discussed above. Lee et al also teach the first region is at one end of the probe (e.g., one end is immobilized to the electrode; page 4, line 35-page 14, line 2).

Regarding claim 49, the detector of claim 47 is discussed above. Sorge et al also teach the third region is at the second end (Figure 3G).

Regarding claim 50, the detector of claim 45 is discussed above. Lee et al also teach the electrode comprises a metal (page 8, lines 15-21).

8. Claims 43 and 51-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) and of Sorge et al (U.S. Patent No. 6,350,580, issued 26 February 2002) as applied to claims 42 and 50 above, and further in view of Hashimoto (U.S. Patent Application Publication No. US 2001/0024788 A1, issued 27 September 2001).

Regarding claims 43 and 51, the detector of claims 42 and 50 are discussed above. While Lee et al also teach the electrode comprises a metal (page 8, lines 15-21), Lee et al and Sorge et al are silent with respect to gold.

However, Hashimoto teaches a nucleic acid carrier for electric detection of nucleic acids (Abstract) comprising gold electrodes and immobilized thiolated nucleic acids with the added advantage that gold is preferable for immobilizing sulfur-bearing nucleic acids because of the high affinity of gold for sulfur (paragraph 0032).

It would therefore have been obvious to a person or ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al and Sorge et al with the gold electrodes as taught by Hashimoto with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in high affinity immobilization of nucleic acids to the electrodes as explicitly taught by Hashimoto (paragraph 0032).

Regarding claim 52, the detector of claim 51 is discussed above. Lee et al also teach the redox moiety is ethidium bromide (page 15, lines 5-15).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert T. Crow
Examiner
Art Unit 1634

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER

Notice to Comply	Application No. 10/678,760	Applicant(s) Heeger et al	
	Examiner Robert T. Crow	Art Unit 1634	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Nucleic acid sequences listed in the Specification lack SEQ ID Nos.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510
For CRF Submission Help, call (571) 272-2501/2583.
PatentIn Software Program Support
Technical Assistance..703-287-0200
To Purchase PatentIn Software.........................703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY